

Characterization of D-Mannitol by Thermal Analysis, FTIR, and Raman Spectroscopy

D-mannitol is a common excipient used in the pharmaceutical formulation of tablets. It is often desirable to process the formula into an amorphous glassy state to improve some physical or biological properties of the drug. The glass property of D-mannitol, e.g., the glass transition temperature, T_g , therefore plays a key role in formulation development.

Differential scanning calorimetry (DSC) is the classical tool used to study the thermodynamic properties of materials, including the glass transition (T_g). The melting behavior of D-mannitol has been studied by DSC.^{1,2} When D-mannitol is cooled from its molten state, it can be easily crystallized. Therefore, it is difficult to get a glassy state of D-mannitol by cooling in conventional DSC because of the slow cooling rate. Previously, the D-mannitol glass was achieved by quenching the molten outside of the DSC, for example, by contact with a -80 to -85 °C metal block for approximately 30 sec. Subsequent heat scanning from -30 °C at 7 °C/min was used to detect the glass transition. However, it is still difficult to obtain a well-defined glass transition because D-mannitol shows an immediate cold crystallization right after the glass transition, which makes the accurate determination of glass transition impossible.³ Since the T_g of D-mannitol cannot be measured directly in conventional DSC, it has to be inferred from other data, for example, by estimation from

the melting point using a variety of scaling rules,⁴ or by introducing a small amount of sorbitol as an impurity to delay the D-mannitol crystallization and extrapolating the T_g of the mixture to zero sorbitol concentration to obtain the T_g of the pure D-mannitol.³

One recent development of advanced DSC technologies is the fast-scan DSC technology pioneered by the HyperDSC[®] technique (PerkinElmer LAS, Shelton, CT). With HyperDSC, it is possible to scan at a much faster rate for both heating and cooling. The fast scanning rate not only increases the sensitivity of the measurement, but also suppresses many kinetic events such as cold crystallization, which may interfere with the measurement. Since introduction of the technique, many new applications in the polymer and pharmaceutical industries have been found that were previously impossible.⁵⁻¹⁶ This article describes the use of HyperDSC to characterize the glass transition of D-mannitol.

D-mannitol also exhibits complex polymorphic behaviors. Polymorphism refers to the different crystalline forms of the same molecule. Many drugs or excipients can exist in multiple crystalline forms. The polymorphic form can have a profound impact on the physicochemical properties of the substance. D-mannitol has three common polymorphic forms with different thermodynamic stability.¹⁷ Polymorphs can be identified by several dif-

ferent techniques. Here, FTIR and Raman spectroscopy were used to identify different polymorphic forms of D-mannitol.

Experimental

Materials

D-mannitol (99+%) was obtained from Sigma Aldrich (St. Louis, MO) and used without further purification.

DSC measurement

The DSC experiment was performed on the PerkinElmer Diamond DSC instrument using the HyperDSC technique. The instrument was equipped with a liquid nitrogen cooling accessory with helium as the purge gas. The instrument was calibrated using indium at 10 °C/min. A D-mannitol sample was prepared in a standard aluminum pan. The sample was melted first at 200 °C and then cooled at several different rates to -30 °C and subsequently heated at several different rates up to 500 °C/min.

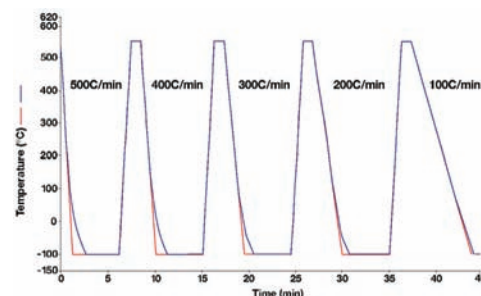


Figure 1 Sample temperature signal vs time at several different cooling rates on Diamond DSC.

FTIR measurement

The FTIR experiment was performed using a **PerkinElmer** Spectrum™ 100 FTIR spectrometer. Samples were measured using attenuated total reflection (ATR) on a single bounce diamond/ZnSe ATR crystal.

All samples were measured between a frequency range of 4000 to 650 cm^{-1} . Each was collected at 4 cm^{-1} resolution with Strong Beer-Norton apodization. A total of 16 background and sample scans were measured for each sample. Data were collected with a temperature-stabilized deuterated triglycine sulfate (DTGS) detector. The three different crystalline forms of D-mannitol were measured separately by placing the sample in contact with the ATR crystal and by applying force from the pressure applicator supplied with the ATR accessory. The application of pressure enabled the sample to be in intimate contact with the ATR crystal, ensuring a high-quality spectrum was achieved.

Raman measurement

The Raman experiment was performed with a **PerkinElmer** RamanStation™ 400 benchtop Raman spectrometer, an Echelle-based system that has no moving part within the spectrograph. The system is able to achieve 4 cm^{-1} resolution across a measurement range of 95–3500 cm^{-1} Raman shift. The system uses an open electrode silicon base charged-coupled device (CCD, 1024 × 255 pixels) detector that is thermostatically controlled to $-50\text{ }^{\circ}\text{C}$. The system is fitted with a 300-mW 785-nm near-infrared laser, which delivers 100 mW of power at the sample with a 100- μm spot size. The three different D-mannitol crystalline forms were measured directly using 100 mW of power and 100- μm spot size. Samples were measured between 200 and 3200 cm^{-1} Raman shift at 4 cm^{-1} resolution. A total of 16 sec of collection time was used.

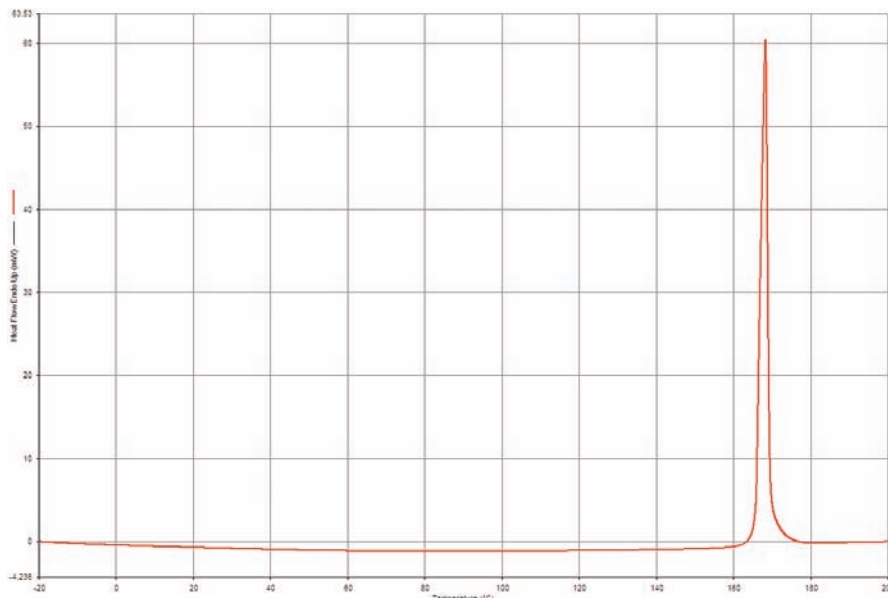


Figure 2 DSC curve of D-mannitol heating at 10 $^{\circ}\text{C}/\text{min}$.

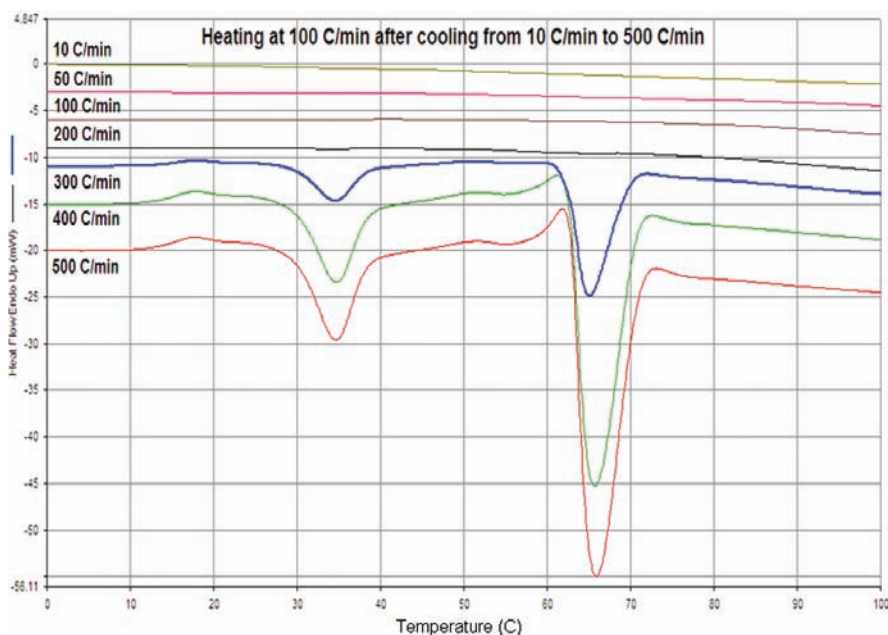


Figure 3 DSC heating curve at 100 $^{\circ}\text{C}/\text{min}$ after cooling from 10 $^{\circ}\text{C}/\text{min}$ to 500 $^{\circ}\text{C}/\text{min}$.

Results and discussion

HyperDSC is a premier fast-scan DSC technology performed only on power compensation DSC. With HyperDSC, valid DSC measurements can be made with a scanning rate up to 500 $^{\circ}\text{C}/\text{min}$ covering a broad temperature range, as seen in *Figure 1*. The figure shows measured sensor temperature (blue curve) and program temperature (red) as functions

of time. Conventional DSC is incapable of heating at rates approaching 500 $^{\circ}\text{C}/\text{min}$ or realizing a constant cooling rate higher than 20 $^{\circ}\text{C}/\text{min}$ over a broad temperature range. Of course, both of these capabilities are important for accurate fast-scan measurements. In *Figure 1*, all heating ramps were performed at a rate of 500 $^{\circ}\text{C}/\text{min}$. In every case, the sample temperature (blue curve) and program temperature (red) as functions of time coincided with the programmed temperature very well. For

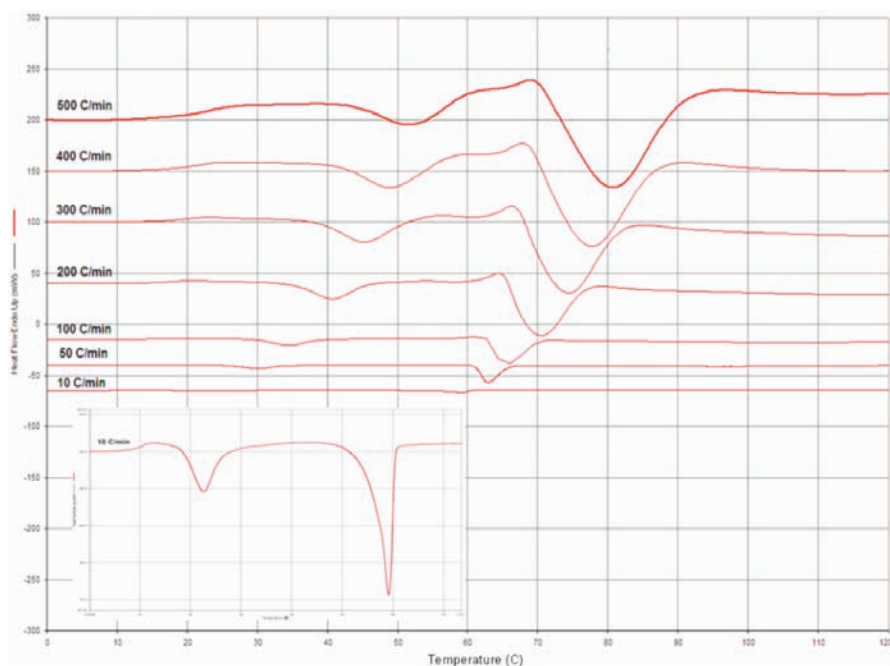


Figure 4 DSC heating curve from 10 °C/min to 500 °C/min after quenching at 500 °C/min.

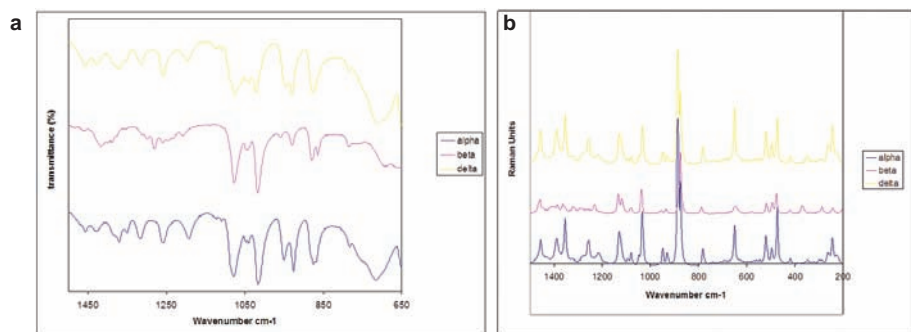


Figure 5 a) FTIR spectroscopy of D-mannitol. b) Raman spectroscopy of D-mannitol.

the cooling experiment, several different cooling rates were used from 100 °C/min to 500 °C/min. The results obtained in the cooling scans demonstrate the exceptional cooling capability of HyperDSC. Only toward the end of the cooling scan did the sample temperature start to deviate from the program temperature.

The D-mannitol sample was first heated to 200 °C at 10 °C/min. It had a big melting peak with onset at 166 °C. The sample was then cooled down to -30 °C at 10 °C/min and heated again to check for glass transition around 10 °C. Clearly, there was no detectable T_g (Figure 2). The sample was crystallized fully during cooling at 10 °C/min, which is

expected due to its strong tendency to crystallize.

Since quench cooling increases the chance of glass formation and HyperDSC offers the flexibility of cooling at a much higher rate than conventional DSC, quench cooling experiments were performed on the sample to study its effect on the glass formation. The sample was first melted at 200 °C and cooled down to -30 °C at several different rates up to 500 °C/min. It was then heated at 100 °C/min to check for the glass transition. The results are shown in Figure 3. There is no glass formation at a cooling rate up to 200 °C/min. Only at a quenching rate of ≥ 300 °C/min can the sample be quenched into an

amorphous state, and the T_g can be detected during subsequent heating. The higher the quenching rate, the more amorphous material was generated. The heat capacity change during the glass transition after cooling at 500 °C/min was 0.76 J/g* °C compared with the reported value of 1.27 J/g* °C.³ It is clear that only part of the sample was quenched into glass even at a cooling rate of 500 °C/min.

Figure 4 shows the heating curves at several different heating rates after the sample was quenched at 500 °C/min. The cold crystallization right after T_g prevented accurate T_g determination at a conventional scanning rate of 10 °C/min (inset, Figure 4). However, HyperDSC is able to suppress kinetic events such as cold crystallization. The cold crystallization was pushed to a higher temperature so that the T_g measurement became possible as evidenced at 500 °C/min. Another obvious advantage of HyperDSC is the increased signal associated with the high scanning rate. Thus, low-energy transition can be detected more easily with HyperDSC.

D-mannitol has three common polymorphic forms. The D-mannitol received has a β polymorph. δ and α forms were made by cooling down after melt at slow (0.5 °C/min) and fast (10 °C/min) rates, respectively. The selection rules that govern Raman and FTIR spectroscopy are different. Raman spectra feature the symmetrical bonds within the molecule, while FTIR spectra feature bonds that have strong dipole moments. The two techniques together provide unique and complementary insight into the structure of molecules.

Figure 5 shows the FTIR and Raman spectra of three polymorphic forms of D-mannitol. Both FTIR and Raman spectra show the difference among these three polymorphs of D-mannitol due to the varied arrangement of molecules in

the crystals. FTIR demonstrates the obvious difference between 1200 and 1400 cm^{-1} in the C–H deformation vibrations region. In Raman, the difference shows up in the region between 1000 and 1200 cm^{-1} .

Conclusion

Fast-scan DSC technology offers new opportunities for materials characterization. The direct measurement of T_g of D-mannitol is now possible with the efficient cooling and heating capability of HyperDSC. Different polymorphic forms can be identified by FTIR and Raman spectroscopy.

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Dr. Ye is Applications Scientist, and Mr. Byron is Senior Product Specialist, **PerkinElmer LAS**, 710 Bridgeport Ave., Shelton, CT 06484, U.S.A.; tel.: 203-402-1708; fax: 203-944-4928; e-mail: peng.ye@perkinelmer.com.